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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/823,964	04/14/2004	Narendra Bam	PU60053	5460

20462 7590 10/17/2006

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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 10/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/823,964	BAM ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/27/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *2-5,23-28, 30-35, and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-22,29,36-42 and 44-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/22/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-22 and 25-47), and elections of SEQ ID NO: 8 and a polymer of methoxypolyethylene maleimide MW 20kDa in the reply filed on 27 April 2006 is acknowledged. It is noted that a Non-Responsive Notice was sent out on 6/23/2006 for failure to make the additional required elections. Applicant telephoned the Examiner on 6 July 2006 to point out specifically where the information could be found in the reply, filed 27 April 2006. The oversight was due to an internal document indexing error and the Examiner was able to locate the statement of further election, originally submitted by Applicant on 27 April 2006.

Formal Matters

2. Claims 1-47 are pending. Claims 2-5, 23-28, 30-36 and 43 are withdrawn as being drawn to non-elected inventions. Claims 1, 6-22, 29, 37-42, and 44-47 are under examination as they read in SEQ ID NO: 8 and a polymer of methoxypolyethylene maleimide (also known as mPEG) MW 20kDa.

Specification - Objections

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (p. 7, line 4). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

4. Claims 21 and 22 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 21 recites the composition as claimed in claim 17 wherein the composition is PEGylated native human IL-18 (SEQ ID NO:1). However, claim 17, is dependent on a series of claims that go back to independent claim 9, which recites only human IL-18 substitution mutants and fails to recite native human IL-18 or SEQ ID NO: 1. Claim 22 is objected to as being dependent on claim 21 and for reciting SEQ ID NO:1 where SEQ ID NO:1 is not part of the independent claim or preceding dependent claims.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 7-22, 29, 37-42, and 44-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the human IL-18 (SEQ ID NO: 1) PEGylated at C38 and/or C68 and the human IL-18 mutant (SEQ ID NO: 8) PEGylated at residue D157C, does not reasonably provide enablement for the other claimed human IL-18 PEGylated proteins and mutants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims recite a human IL-18 substitution mutant wherein said mutant comprises from one to five amino acid substitutions in the sequence of SEQ ID NO: 1, said substitutions being at from one to five amino acid residues chosen from the group [consisting] of the cysteine at residue 38, the cysteine at residue 68, the cysteine at residue 76, the asparagine at residue 78, the glutamic acid at residue 121, the cysteine at residue 127, the leucine at residue 144, and the aspartic acid at residue 157; wherein said mutant [comprises] a serine in place of the cysteine at residue 38, an aspartic acid in place of the cysteine at residue 68, and a cysteine in place of aspartic acid at residue 157 (SEQ ID NO: 8); a biologically active composition comprising a polypeptide conjugated to a water-soluble polymer wherein the polypeptide is human IL-18 (SEQ ID NO: 1); a biologically active composition comprising a polypeptide conjugated to a water-soluble polymer wherein the polypeptide is a human IL-18 substitution mutant chosen from the group of: SEQ ID NO: 8 [as elected]; wherein the conjugation between the polypeptide and the polymer is covalent; wherein the water-soluble polymer is a member chosen from the recited group; wherein the water-soluble polymer is unsubstituted; wherein the water-soluble polymer is substituted at one end with an alkyl group; wherein the water-soluble polymer is a polyethylene glycol homopolymer; wherein the

polyethylene glycol homopolymer is a monomethoxy-polyethylene glycol; wherein the monomethoxy-polyethylene glycol is chosen from the group of linear and branched monomethoxy-polyethylene glycol; wherein the PEG homopolymer has a molecular weight of from about 20kDa to 40 kDa; wherein the PEG homopolymer has a molecular weight of about 20kDa; wherein the PEG homopolymer has a molecular weight of about 30kDa; wherein the PEG homopolymer has a molecular weight of about 40kDa; the composition of claim 17 wherein the composition of PEGylated native human IL-18 (SEQ ID NO: 1); wherein the native human IL-18 (SEQ ID NO: 1) is PEGylated at the cysteine at residue 38 and at the cysteine at residue 68; wherein the human IL-18 substitution mutant has the amino acid sequence set forth in SEQ ID NO: 8 and wherein the mutant is conjugated water-soluble polymer at the cysteine at residue 157; a method of preparing a biologically active composition comprising obtaining a human IL-18 polypeptide (SEQ ID NO: 1) and contacting the polypeptide with a functionalized water-soluble polymer; a method of preparing a biologically active composition comprising obtaining a human IL-18 substitution mutant polypeptide selected from SEQ ID NO: 8 [as elected] and contacting the polypeptide with a functionalized water-soluble polymer; the method wherein the functionalized water soluble polymer is chosen from methoxypolyethylene glycol maleimide, MW 20kDA; the product made by the method of claim 36; the product made by the method of claim 37; a method of improving the pharmacokinetics and pharmacodynamics of human IL-18 (SEQ ID NO: 1) comprising the step of conjugating the human IL-18 (SEQ ID NO: 1) to a water-soluble polymer; a method of improving the pharmacokinetics and pharmacodynamics of a human IL-18 substitution mutant (SEQ ID NO: 8) [as elected] comprising the step of conjugating the human IL-18 substitution mutant to a water-soluble polymer; wherein the subcutaneous bioavailability is improved; wherein the subcutaneous bioavailability is improved and binding to IL-18BP is reduced.

The nature of the invention is drawn to PEGylated human IL-18 and PEGylated human IL-18 substitution mutants, methods of making the PEGylated proteins, and methods of improving their pharmacokinetics through PEGylation. Proteins modified by the covalent attachment of water-soluble polymers such as polyethylene glycol, copolymers of polyethylene glycol and polypropylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinylpyrrolidone or polyproline are known to exhibit substantially longer half-lives in blood following intravenous injection than do the corresponding unmodified proteins (see generally, Katre et al., PNAS USA 1987; 84:1487-1491). Such modifications may also increase the protein's solubility in aqueous solution, eliminate or decrease aggregation, enhance the physical and chemical stability of the protein, and greatly reduce the immunogenicity and antigenicity of the protein. As a result, in certain embodiments, the desired in vivo biological activity may be

achieved by the administration of such polymer-protein adducts less frequently or in lower doses than with the unmodified protein (Id).

The scope of the patent protection sought by Applicant as defined by the claim fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons. It is unclear from the claims or the disclosure whether the claimed human IL-18 substitution mutant will be functionally active. The state of the art discloses that PEGylated interleukin proteins can be non-functional or the biological activity can be greatly reduced, depending on where the PEG moiety is added to the protein (see, i.e. Pettit et al., J Biol Chem 1997 272(4):2312-2318, especially p. 2312, Abstract). A large PEG moiety can also interfere with ligand-receptor binding (Pettit et al., *supra*, abstract). Defined positioning of a water-soluble moiety on a cytokine, like IL-18, is critical if biological activity is to be maintained. For example, Kirkpatrick et al., (Protein Expr Purif 2003 Feb;27(2):279-92) teach that the N-terminal tyrosine of IL-18 is critically important for biological activity (p. 285, column 2 and 287, column 2, third paragraph). However, N-terminal PEG additions have better *in vivo* effects and there is less risk of loss of biological activity of the proteins due to steric interference with binding sited by the attached PEG-moiety (see generally, Drummond et al., WO 99/45026 (published 10 September 1999). As such, the teachings of Kirkpatrick et al., and Drummond et al., indicate that random attachment of a water-soluble polymer to an IL-18 protein (wild-type or substitution mutant) through a method of merely contacting the polypeptide with the water-soluble polymer would not necessarily produce a PEGylated ligand capable of binding its receptors.

Further, the production of IL-18 generally requires a pro-domain to retain full activity (p. 289, column 2, last paragraph). This is thought to be due to improper folding in the absence of the pro-domain region (p. 289, column 2, last paragraph). Additionally, Fu et al., (Acta Biochimica et Biophysica Sinica 2001; 33(4):368-372) teach that D126, D130 and D134 are necessary for human IL-18 to elicit IFNγ production from PBMCs and Kim et al., (J Biol Chem 29 March 2992; 277(13):10998-11003) teach identification of amino acid residues critical for biological activity in human IL-18, which include E42 and K89. The teachings of Kim et al., provide motivation for Applicants to mutate and/or PEGylates residues near E42 and K89 of SEQ ID NO: 1 (wild-type IL-18) because point mutations at or near these sites were shown to destabilize the three-dimensional structural integrity of IL-18 and interfere with IL-18 binding to IL-18BP (Kim et al., p. 10998, abstract, and p. 11002, second column, second paragraph). Whether point mutations and/or addition of a water-soluble polymer would interfere with IL-18 receptor or IL-18BP binding is unpredictable because of the three dimensional confirmation of IL-18, which has been shown to become structurally destabilized due to point mutations (see Kim et al., *supra*, entire

document). Large water-soluble moieties added at or near critical binding sites would likely sterically interfere with the three-dimensional structure of IL-18 and could also interfere with receptor binding. Additionally, the pharmacokinetics and bioavailability of IL-18 conjugated to water-soluble moieties would be unpredictable without knowing whether the structural integrity of the protein were changed due to point mutations or the addition of water-soluble polymers at or near residues that are critical for receptor binding.

The skill of those in the art is high with respect to the chemical/biotech techniques to PEGylate proteins such as IL-18. Although the coupling of water-soluble polymers to proteins is well known in the art, a high level of skill is required in order to construct mutated PEGylated proteins that retain a high degree of biological activity. The activity/function of the resulting PEGylated protein is unpredictable, particularly when the protein is mutated to facilitate PEGylation.

Example 1 of the instant disclosure recites a prediction of PEGylation sites based on human and murine IL-18 crystal structures of SEQ ID NO:1 (wild-type human IL-18) (p. 17). Example 2 recites substitution mutant designs whereby the crystal structure of the murine IL-18 was used to determine a PEGylation strategy that placed the PEG moiety away from the receptor binding site (pp. 17-18). Wild-type human IL-18 contains four cysteine residues. Two of those, C38 and C68, are accessible for PEGylation, as predicted by the crystal structure, but exhibited reduced biological activity when tested in vivo (see specification, p. 18, lines 1-5 and Table 1). Table 1 (p. 20) shows that PEGylation of SEQ ID NO: 8 at D157C resulted in increased biological activity, but that was not the case with all of the IL-18 mutants tested. Table 1 also shows PEGylated wild-type human IL-18 (SEQ ID NO: 1), PEGylated at C38 and/or C68, as being biologically active, but with significantly reduced biological function compared to the non-PEGylated wild-type human IL-18. As a result, although Applicant is enabled for PEGylated wild-type human IL-18 (SEQ ID NO: 1), PEGylated at C38 and/or C68, and the human IL-18 mutant consisting of SEQ ID NO: 8 PEGylated at residue D157C, undue experimentation would be required to determine whether the other claimed human IL-18 PEGylated mutants with one to five amino acid substitutions are biologically active. Table 1 only shows 8 PEGylated cites and only one of those mutated sites are from the SEQ ID NO: 8 mutant.

Several of the claims are excessively broad. For example, claims 7 and 8 recite a composition comprising a peptide conjugated to a water-soluble polymer wherein the polypeptide is human IL-18. The claim is not limited to a specific polymer nor is the placement of the polymer on the protein contemplated by the claim. Similarly, claims 9 and 10 recite a specific IL-18 mutant, but fail to define a specific polymer or the placement of the polymer on the protein.

Further, the preamble of claims 7 and 9 does not carry patentable weight. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). The claims, as written, recite a biologically active composition comprising a polypeptide. The claims do not limit the biological activity of the composition to the claimed polypeptide (i.e. other components of the composition may be the biologically active ingredients), nor do the claims, as written, require that the polypeptide, itself, be biologically active.

Therefore, based on the discussions above concerning the art's recognition that defined positioning of a water-soluble moiety on a cytokine like IL-18 is critical if biological activity is to be maintained and that PEGylated interleukin proteins can be non-functional or the biological activity can be greatly reduced, depending on where the PEG moiety is added to the protein, the specification fails to teach the skilled artisan how to use the claimed methods without resorting to undue experimentation to determine whether the other claimed PEGylated human IL-18 mutant proteins are biologically active.

Due to the large quantity of experimentation necessary to determine the biological activity of all of the claimed PEGylated human IL-18 mutant proteins, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that PEGylated interleukin proteins can be non-functional or the biological activity can be greatly reduced if the PEG moiety is improperly positioned, and the breadth of the claims which fail to recite where the PEG moiety is to be positioned in order for the claimed protein to retain functional activity, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 22 and 29 are rejected for being dependent on rejected claims.

Claim Rejections - 35 USC § 112, Second Paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 7 and 9 recite the limitation "biologically active composition" in the preamble of the claim. The

specification fails to the metes and bounds for what a biological active composition is supposed to be. The preamble of the claims do not impart a requirement for "biological activity" to human IL-18 or the human IL-18 substitution mutant. Further, it is unclear what the biological activity is supposed to be. Is binding to a receptor sufficient biological activity? Claim 8 is rejected as being dependent on claim 7. Claim 10 is rejected as being dependent on claim 9.

9. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is a word missing between the words "group" and "of" in line 3. It is unclear whether the Applicant intends the claim to recite "...the group consisting of..." or "...the group comprising..." to mean "comprising" or "consisting".

10. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "contains" in line 2 is a non-standard word. It is unclear whether the Applicant intends the claim to recite "wherein said mutant comprises a serine..." or "wherein said mutant consists of a serine...."

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Yamamoto et al., EP 845530 A3 (published 3 June 1998) (see especially, SEQ ID NO: 7 and claim 5).

The claims recite a human IL-18 substitution mutant wherein said mutant comprises from one to five amino acid substitutions in the sequence of SEQ ID NO: 1, said substitutions being at from one to five amino acid residues chosen from the group [consisting] of the cysteine at residue 38, the cysteine at

residue 68, the cysteine at residue 76, the asparagine at residue 78, the glutamic acid at residue 121, the cysteine at residue 127, the leucine at residue 144, and the aspartic acid at residue 157.

Yamamoto et al., teach a human IL-18 substitution mutant comprising from one to five amino acid substitutions in the sequence of instant SEQ ID NO: 1, said substitutions being from one to five amino acid residues, comprising the cysteine at residue 38 and the cysteine at residue 68 (see Yamamoto et al., SEQ ID NO: 7 and claim 5).

13. Claims 7 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Tamarkin et al., US Patent 6,274,552 (14 August 2001).

The claims recite a biologically active composition comprising a polypeptide conjugated to a water-soluble polymer wherein the polypeptide is human IL-18 (SEQ ID NO: 1); wherein the conjugation between the polypeptide and the polymer is covalent.

Tamarkin et al., teach compositions comprising biologically active factors, including IL-18 (column 7, line 38) covalently bound to colloidal gold and stabilized by the addition of polyethylene glycol (column 9, lines 4-24).

14. Claims 7, 8, 36, 39, 41 and 44 are rejected under 35 U.S.C. 102(e) as being anticipated by Burton et al., US PreGrant Publication US 2004/0136992 (15 July 2004, benefit to 28 August 2002).

The claims recite a biologically active composition comprising a polypeptide conjugated to a water-soluble polymer wherein the polypeptide is human IL-18 (SEQ ID NO: 1); wherein the conjugation between the polypeptide and the polymer is covalent; wherein the water-soluble polymer is a member chosen from the recited group; wherein the water-soluble polymer is unsubstituted; wherein the water-soluble polymer is substituted at one end with an alkyl group; wherein the water-soluble polymer is a polyethylene glycol homopolymer; wherein the PEG homopolymer has a molecular weight of from about 20kDa to 40 kDa; wherein the PEG homopolymer has a molecular weight of about 20kDa; wherein the PEG homopolymer has a molecular weight of about 30kDa; wherein the PEG homopolymer has a molecular weight of about 40kDa; the composition of claim 17 wherein the composition of PEGylated native human IL-18 (SEQ ID NO: 1); a method of preparing a biologically active composition comprising obtaining a human IL-18 polypeptide (SEQ ID NO: 1) and contacting the polypeptide with a functionalized water-soluble polymer; the product made by the method of claim 36; a method of improving the pharmacokinetics and pharmacodynamics of a human IL-18 comprising the step of

conjugating the human IL-18 to a water-soluble polymer; the method of claim 41 wherein the subcutaneous bioavailability is improved.

Burton et al., teach a composition and a method of preparing a biologically active composition comprising human IL-18 and covalent derivatives prepared by linking chemical moieties, such as polyethylene glycol, to functional groups (paragraph 143). Increased pharmacokinetics and bioavailability are taught at paragraphs 143-146. Compositions administered by injection and transdermally are taught at paragraph 221. Covalent derivatives are taught at paragraph 143. IL-18 amino acid substitution mutants, including cysteine mutants and inactivation of N-glycosylation sites, are taught at paragraph 143.

Claim 21 would also be anticipated by Burton et al., if the dependency of the claim is corrected to depend from claim 7, as stated *supra*.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burton et al., US PreGrant Publication US 2004/0136992 (15 July 2004, benefit to 28 August 2002) in view of Martinez et al., US PreGrant Publication US 2004/0062746 A1 (1 April 2004, benefit to 12 December 2002) in further view of Benjamin et al., (Ann Rev Immune 1984 2:67-101).

The claims recite a method of preparing a biologically active composition comprising obtaining a human IL-18 polypeptide (SEQ ID NO: 1) and contacting the polypeptide with a functionalized water-soluble polymer; a method of preparing a biologically active composition comprising obtaining a human IL-18 substitution mutant polypeptide selected from SEQ ID NO: 8 [as elected] and contacting the polypeptide with a functionalized water-soluble polymer; the method wherein the functionalized water soluble polymer is chosen from methoxypolyethylene glycol maleimide, MW 20kDA; the product made by the method of claim 36; the product made by the method of claim 37.

Burton et al., teach (as stated *supra*) a composition and a method of preparing a biologically active composition comprising human IL-18 and covalent derivatives prepared by linking chemical moieties, such as polyethylene glycol, to functional groups (paragraph 143). Increased pharmacokinetics and bioavailability are taught at paragraphs 143-146. Compositions administered by injection and transdermally are taught at paragraph 221. Covalent derivatives are taught at paragraph 143. IL-18 amino acid substitution mutants, including cysteine mutants and inactivation of N-glycosylation sites, are taught at paragraph 143. Burton et al., do not teach mPEG.

Martinez et al., (2004/0062746) teach conjugation of polyalkylene glycols, specifically PEG, monomethoxypolyethyleneglycol (paragraphs 28-31, 67-72) and mPEG (paragraph 187) to IL-18 (paragraph 82). Polymers of various molecular weights are taught including from about 20kDa to about 40kDa, about 20kDa, about 30kDa, and about 40kDa (paragraphs 73 and 76). Pharmaceutical compositions are taught at paragraphs 121-123. Numerous polymers suitable for conjugation including substituted and unsubstituted PEG, mPEG, linear and branched monomethoxyPEG, and monohydroxyPEG, are taught at paragraphs 28-31, 67-72 160 (Example 1), and 184 (Example 7).

Benjamin et al., teach that the surface of proteins consist of a complex array of overlapping potential antigenic determinants (p. 94, last paragraph).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Burton et al., with the teachings of Martinez et al., because Burton et al., teach that IL-18 derivatives can be conjugated with polymer moieties and Martinez et al., teach that numerous polymers are suitable for conjugating purposes. Further, Benjamin et al., teach

that the surface of any protein consists of overlapping antigenic determinants. The person or ordinary skill would have reasonably would have expected success because although the claimed method steps of contacting of the claimed IL-18 substitution mutant polypeptide with a water-soluble polymer would not necessarily produce a biologically active PEGylated polypeptide, the PEGylated polypeptide would be comprised within a biologically active composition because of the antigenic response that would be achieved by administering the PEGylated polypeptide *in vivo*. Further, the claims, as written, provide no limitation regarding where the PEG-moiety should be placed on the polypeptide or whether the PEGylated polypeptide needs to be biologically functional.

19. Claim 41-42, 44-45, and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burton et al., US PreGrant Publication US 2004/0136992 (15 July 2004, benefit to 28 August 2002) in view of Martinez et al., US PreGrant Publication US 2004/0062746 A1 (1 April 2004, benefit to 12 December 2002) in further view of Kim et al., (J Biol Chem 29 March 2992; 277(13):10998-11003).

The claims recite a method of improving the pharmacokinetics and pharmacodynamics of human IL-18 (SEQ ID NO: 1) comprising the step of conjugating the human IL-18 (SEQ ID NO: 1) to a water-soluble polymer; a method of improving the pharmacokinetics and pharmacodynamics of a human IL-18 substitution mutant (SEQ ID NO: 8) [as elected] comprising the step of conjugating the human IL-18 substitution mutant to a water-soluble polymer; wherein the subcutaneous bioavailability is improved; wherein the subcutaneous bioavailability is improved and binding to IL-18BP is reduced.

Burton et al., teach (as stated *supra*) a composition and a method of preparing a biologically active composition comprising human IL-18 and covalent derivatives prepared by linking chemical moieties, such as polyethylene glycol, to functional groups (paragraph 143). Increased pharmacokinetics and bioavailability are taught at paragraphs 143-146. Compositions administered by injection and transdermally are taught at paragraph 221. Covalent derivatives are taught at paragraph 143. IL-18 amino acid substitution mutants, including cysteine mutants and inactivation of N-glycosylation sites, are taught at paragraph 143. Burton et al., do not teach mPEG.

Martinez et al., (2004/0062746) teach conjugation of polyalkylene glycols, specifically PEG, monomethoxypolyethyleneglycol (paragraphs 28-31, 67-72) and mPEG (paragraph 187) to IL-18 (paragraph 82). Polymers of various molecular weights are taught including from about 20kDa to about 40kDa, about 20kDa, about 30kDa, and about 40kDa (paragraphs 73 and 76). Pharmaceutical compositions are taught at paragraphs 121-123. Numerous polymers suitable for conjugation including

substituted and unsubstituted PEG, mPEG, linear and branched monomethoxyPEG, and monohydroxyPEG, are taught at paragraphs 28-31, 67-72 160 (Example 1), and 184 (Example 7).

Kim et al., teach that IL-18 binds and neutralizes IL-18BP biological activity (p. 10998, column 2, third paragraph). Kim et al., also teach that E42 and K89 of wild-type human IL-18 (i.e. SEQ ID NO: 1) are critical amino acid residues for the integrity of IL-18 structure and are important for binding to cell surface receptors, for signal transduction, and for neutralization by IL-18BP (p. 10998, abstract). The binding of wild-type IL-18 and its various mutants was evaluated by competition assays (p. 10998, abstract and p. 11000, column 1).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Burton et al., with the teachings of Martinez et al., because Burton et al., teach that IL-18 derivatives can be conjugated with polymer moieties and Martinez et al., teach that numerous polymers are suitable for conjugating purposes. Further, Kim et al., teach that E42 and K89 of wild-type human IL-18 (i.e. SEQ ID NO: 1) are critical amino acid residues for IL-18 neutralization by IL-18BP. Attaching a large PEG or mPEG moiety near E42 or K89 would sterically interfere with IL-18BP binding. Reduction in binding of IL-18 could easily be tested with competition assays, as taught by Kim et al. The person of ordinary skill would have reasonably would have expected success because Burton et al., teach improved pharmacokinetics and subcutaneous bioavailability in proteins, including IL-18, that are conjugated to water-soluble polymers. Because Kim et al., teach that E42 and K89 of wild-type IL-18 are critical to IL-18BP binding, any steric interference with the ability of IL-18BP to bind, near E42 and/or K89 will result in reduced IL-18BP.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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